Gender and racial disparities in adherence to statin therapy: A meta-analysis

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Background Significant disparities exist in cardiovascular outcomes based on race/ethnicity and gender. Rates of evidence-based medication use and long-term medication adherence also appear to be lower in racial subgroups and women but have been subject to little attention. Our objective was to evaluate the effect of race/ethnicity and gender on adherence to statin therapy for primary or secondary prevention.

Methods and results Studies were identified through a systematic search of MEDLINE, EMBASE, ClinicalTrials.gov, and the Cochrane Database of Systematic Reviews (through April 1, 2010) and manual examination of references in selected articles. Studies reporting on adherence to statins by men and women or patients of white and nonwhite race were included. Information on study design, adherence measurement, duration, geographic location, sample size, and patient demographics was extracted using a standardized protocol. From 3,022 potentially relevant publications, 53 studies were included. Compared with men, women had a 10% greater odds of nonadherence (odds ratio 1.10, 95% confidence interval [CI], 1.07-1.13). Nonwhite race patients had a 53% greater odds of nonadherence than white race patients (odds ratio 1.53, 95% CI 1.25-1.87). There was significant heterogeneity in the pooled estimate for gender (I^2 0.95, *P* value for heterogeneity <.001) and race (I^2 0.98, *P* value for heterogeneity <.001). The overall results remained unchanged in those subgroups that had significantly less heterogeneity.

Conclusions Among patients prescribed statins, women and nonwhite patients are at increased risk for nonadherence. Further research is needed to identify interventions best suited to improve adherence in these populations. (Am Heart J 2013;165:665-678.e1.)

Large differences in cardiovascular outcome rates have been documented based on race, ethnicity, and gender.[1] For example, 1-year mortality rates for black patients with acute myocardial infarction (MI) are 12% to 35% higher than those for white patients, even after adjusting for socioeconomic status (SES), age, gender, comorbidity, and illness severity.[2] In-hospital mortality is >30% higher for women than for men before age 55 years.[3] These patterns have been attributed to differences in the use of evidence-based therapies[4,5] such as percutaneous coronary intervention[6] and bypass surgery.[7]

Rates of evidence-based medication use and long-term medication adherence also appear to be lower in racial subgroups and women but have been subject to little attention.[8,9] Medicare beneficiaries of black race have a 67% higher odds of discontinuing statin therapy than patients of white race,[8] and women concomitantly using antihypertensive and lipid-lowering therapy have a 10% lower odds of adherence than men.[9] These differences are likely to be clinically significant as the appropriate use of cardiovascular medications reduces rates of adverse health outcomes, mortality, and spending.[10-13]

Although the relationship between sociodemographic factors and adherence has been documented, we sought to understand the consistency of these relationships and quantify their magnitude, as nonadherence may be an important contributor to disparities in cardiovascular outcomes that is potentially amenable to intervention. Accordingly, we systematically reviewed the peer-reviewed scientific literature for studies presenting data on the relationship between race, gender, and statin adherence. We focused on this class of medications because of its central role in cardiovascular risk reduction[14,15] and because of the large number of published studies evaluating potential predictors of its use.

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Methods

We performed an electronic search of Medline, EMBASE, ClinicalTrials.gov, and the Cochrane Database of Systematic Reviews through April 1, 2010, for studies that reported adherence to statins.

Search strategy

Our electronic search strategy included medical subject headings (MESH) and keywords related to medication adherence (eg, "adherence," "compliance," "non-adherence," "non-compliance," "treatment refusal," "persistence"), adherence measures (eg, "medication monitoring," "pill count"), adherence predictors (eg, "predictor," "barriers," "risk factors"), statins (eg, "statins," "anti-cholesterol," "HMG CoA reductase inhibitor"), race, ethnicity, and gender. The full search strategy is available in the online Appendix.

Study selection

Using predefined inclusion and exclusion criteria, 2 investigators (A.D.K.B. and E.K.) independently reviewed the electronic search results to identify potentially relevant articles. Disagreements were resolved by consensus. Published versions of candidate articles were retrieved, and their reference lists reviewed to identify other studies that our search strategy may have missed. We included studies that evaluated adherence to statins and reported on gender, race, or ethnicity as a predictor of adherence in univariable or multivariable analysis. We excluded studies that did not (1) present quantitative measures of adherence; (2) present original data; (3) evaluate gender, race, or ethnicity as a predictor of adherence; or (4) evaluate statin use. Studies that reported adherence to statins and another medication (eg, another lipid-lowering therapy or antihypertensive) were included, even if the entire cohort was not exposed to statin therapy.

Data abstraction

Data on patient and study characteristics, outcomes, and study quality were extracted in duplicate using a standardized protocol and reporting form. We collected information on study design (eg, cohort, cross-sectional, or randomized control trial), duration, geographic location, sample size, and patient demographics. We also recorded the method of adherence measurement (eg, pharmacy claims refill data, self-report, pill count, or medication event monitoring system). For studies with incomplete quantitative information, attempts were made to contact study authors to obtain additional data. Study quality was assessed with the Newcastle Ottawa Quality Assessment Scale for observational studies.[16] A study quality score was calculated as a proportion of total points that each paper received.

From each study, we extracted the proportion of women (vs men) and nonwhite race patients (vs white race patients) who were nonadherent to their prescribed statin. For studies that defined adherence in more than 1 way, we chose data corresponding to an adherence threshold of 80%, which is widely used in the literature to identify patients who are "fully adherent"[17] and which were based upon "proportion of days covered" or "medication possession ratio" as opposed to "persistence." Race and ethnicity were classified as white versus nonwhite. If adherence data for multiple time points were reported, we used results for 12 months of follow-up.

For studies that reported odds ratios for the relationship between gender or race and adherence but did not also present raw proportions, we back calculated 2-by-2 contingency data with a quadratic equation based upon the total sample size, number of women and men (or nonwhite and white patients, as appropriate), and overall number of adherent and nonadherent patients. Multivariable adjusted odds ratios were preferentially used if available.

Data analysis

The 2 primary outcomes of our analysis were the odds of nonadherence in women as compared with men and in patients of nonwhite race as compared with those of white race. Odds ratios (ORs) and 95% CIs were calculated from each included study. We combined individual study results using a random-effects meta-analysis with Mantel-Haenszel weighting. Studies presenting data on both gender and race were included in both analyses. If studies presented results for both primary and secondary prevention patients, the data were combined and reported in aggregate. Publication bias was assessed using a funnel plot of each trial's effect size against the standard error.

Between-study heterogeneity was explored in several ways. First, we visually inspected the plot of overall adherence proportions to look for outliers. Second, the proportion of the overall variation in nonadherence that was attributable to between-study heterogeneity was estimated with an I^2 statistic.[18] Finally, pooled adherence was calculated in prespecified study subcategories: method of adherence measurement, geographic region, study size, prevention status (primary vs secondary), analytic method (univariable vs multivariable), and adjustment for SES or race/gender, as appropriate. All analyses were conducted using Review Manager version 5.1 (Copenhagen: The Cochrane Collaboration, 2011).

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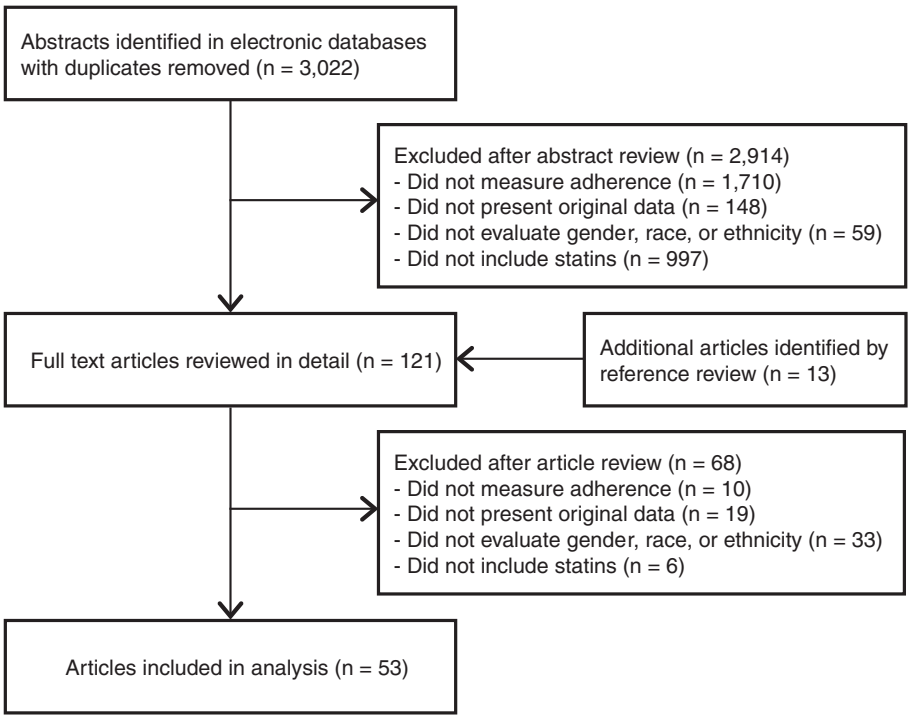
Results

Our search identified 3,022 unique abstracts, of which 53 studies met our inclusion criteria (Figure 1). These studies included a total of 2,663,638 patients (sample size range 83-962,877), and average adherence in all studies was 48%. Among the 53 included studies, 51 evaluated adherence based on gender[8,9,17,19-66] and 11 based on race.[8,20,21,33,41-43,47,65,67,68] The maximum duration of follow-up ranged from 3 to 156 months (average 39 months). Fourteen studies followed subjects for ≥5 years. The studies were predominately conducted in North America, with 55% based in the United States. All of the studies evaluating race were conducted in the United States. Most were cohort studies. Pharmacy refill claims and medical records were used to evaluate adherence in 46 studies. Further details of the study designs and patient demographics are presented in Table I. Funnel plots evaluating adherence based on gender and race indicate no evidence of publication bias.

Figure 1



Flow diagram of study selection.

Gender

Crude rates of nonadherence were higher in women than men (53% vs 50%). Pooled across studies, women were 10% more likely to be nonadherent to their prescribed statin (OR 1.10, 95% CI 1.07-1.13) (Figure 2). Although there was significant heterogeneity in the pooled estimate (I^2 0.95, *P* value for heterogeneity <.001), the increased risk among women persisted in studies using multivariable methods as well as those that adjusted for race and socioeconomic status (Table II). Results did not differ meaningfully in large as compared with small studies or based upon the indication for the prescribed statin (eg, primary vs secondary prevention). Studies that measured adherence by self-report had less heterogeneity (I^2 0.45, *P* value for heterogeneity 0.12) and demonstrated higher odds of nonadherence for women (OR 1.20, 95% CI 1.0-1.44) compared with studies that used pharmacy claims (OR 1.10, 95% CI 1.07-1.13). Studies using pharmacy refill data to measure persistence had a smaller pooled estimate (OR 1.04, 95% CI 0.99-1.10) compared with studies measuring adherence by percentage of days covered (OR 1.12, 95% CI 1.08-1.16). In the 11 studies conducted in Canada, gender appeared unrelated to nonadherence.

Race

Crude rates of nonadherence were higher in patients of nonwhite as compared with white race (50% vs 45%). Pooled across studies, nonwhite patients were 53% more likely to be nonadherent to statin therapy (OR 1.53, 95% CI 1.25-1.87) (Figure 3). Significant heterogeneity was again present in the pooled estimate (I^2 0.98, *P* value for heterogeneity <.001). The four studies that measured adherence by self-report had less heterogeneity (I^2 0.53, *P* value for heterogeneity 0.09) and a similar risk of nonadherence among nonwhite patients (OR 1.56, 95% CI 1.08-2.24) (Table III). The odds of nonadherence were lower but still significantly increased among nonwhites treated in secondary prevention studies (OR 1.28, 95% CI 1.04-1.59) in which there was little between-study heterogeneity (I^2 0.06, *P* value for heterogeneity 0.36). Nonwhites continued to have an increased risk of nonadherence (OR 1.51, 95% CI 1.19-2.02) in the 5 studies that adjusted for socioeconomic status, insurance status, or copayment amount. Nonwhite patients were 67% less adherent than white patients in studies published before 2008 compared to 22% less adherent in studies published in 2008 or later.

Discussion

Racial and gender-based disparities in cardiovascular outcomes have been well described. The reasons for these differences in care are complex, but differences have been documented in the use of invasive

Table I. Study characteristics

Variable evaluated	Source	Sample size	Maximum duration (mo)	Mean age in years (SD)	Country	Design	Adherence measure	Adherence definition	Overall adherence	Prevention status*	Adjustment	Quality score (%)
Gender	Perreault 2005a	20353	42	57.9 (4.6)	Canada	Cohort	Pharmacy records	No medication gap >60 d	50%	Primary	Age, sex, comorbidities, SES, geography, concomitant medications, dosing frequency, health care utilization	100
Gender	Perreault 2009	115290	78	63 (NA)	Canada	Cohort	Pharmacy records	≥80%	62%	Primary	Unadjusted	75
Gender	Blackburn 2005	1221	60	58 (NA)	Canada	Cohort	Pharmacy records	≥80%	54%	Secondary	Unadjusted	75
Gender	Eagle 2004	6320	6	65 (median)	Multicountry	Cohort	Self-report	Persistent use	87%	Secondary	Unadjusted	63
Gender	Holme 2009	8,888	72	61.8 (10.1)	Multicountry	RCT	Pharmacy records	≥80%	89%	Secondary	Unadjusted	75
Gender	Hudson 2007	20239	72	71 (62.8)	Canada	Cohort	Pharmacy records	No medication gap >60 d	75%	Secondary	Unadjusted	75
Gender	Jackevicius 2008	4,591	4	76.3 (NA)†	Canada	Cohort	Pharmacy records	All prescriptions filled within 120 d after AMI	95%	Secondary	Age, sex, SES, comorbidities, concomitant medications, no. of physicians, discharge counseling	100
Gender	McGinnis 2009	2201	84	62.2 (10.6)	USA	Cohort	Pharmacy records	≥80%	59%	Secondary	Age, sex, comorbidities, chronic disease score, LDL tests per year, concomitant medications, cardiovascular events	100
Gender	Rasmussen 2007	17823	12	74.7 (6.2)†	Canada	Cohort	Pharmacy records	≥80%	88%	Secondary	Age, sex, SES, admission year, physician specialty, illness severity, hospitalization, use of index medication before hospitalization, concomitant medications	100
Gender	Shah 2009	219	108	64.5 (14.6)	USA	Cohort	Pharmacy records	No medication gap >90 d	78%	Secondary	Age, sex, comorbidities, smoking status, in-hospital revascularization, enrollment in cardiac rehabilitation program	100
Gender	Ye 2007	5548	12	63 (12.1)	USA	Cohort	Pharmacy records	≥80%	61%	Secondary	Age, sex, copayment, insurance type, year of statin initiation, comorbidities, concomitant medications, cardiologist visit	100
Both	Amin 2009	509	36	57 (11.4)	USA	Cohort	Pharmacy records	>80% for ≥2 medications	70%	Secondary	Unadjusted	75
Both	Khanderia 2008	132	24	65.8 (10.1)	USA	Cross-sectional	Self-report	Score of 0 on the medication adherence scale	55%	Secondary	Age, sex, ethnicity, income, living arrangement, months after surgery, response on behavior questionnaire	88

Table I (*continued*)

Variable evaluated	Source	Sample size	Maximum duration (mo)	Mean age in years (SD)	Country	Design	Adherence measure	Adherence definition	Overall adherence	Prevention status*	Adjustment	Quality score (%)
Both	Kulkarni 2005	1326	12	65.7 (10.5)	USA	Cross-sectional	Self-report	Persistent use of all discharge medications	54%	Secondary	Unadjusted	57
Both	Melloni 2009	1077	3	60 (median)	USA	Cross-sectional	Self-report	Persistent use of all discharge medications	72%	Secondary	Unadjusted	57
Gender	Abraha 2003	39222	54	62.9 (12.5)	Italy	Cohort	Pharmacy records	No gap of >30 days and PDC ≥80%	13%	Both	Age, sex, comorbidities	100
Gender	Avorn 1998	7287	12	NA	Multicountry	Cohort	Pharmacy records	≥80%	35%	Both	Age, sex, comorbidities, concomitant medications, outpatient visits, hospitalized days	100
Gender	Benner 2004	19422	36	NA	USA	Cohort	Pharmacy records	≥80%	43%	Both	Age, sex, income, comorbidities, medical procedures, lipoprotein levels, concomitant medications, outpatient visits, hospitalized days, prior lipid-lowering therapy	100
Gender	Benner 2005	9510	36	60.2 (12.9)	USA	Cohort	Pharmacy records	≥80%	34%	Both	Age, sex, income, comorbidities, initial LDL reduction, initial adherence	100
Gender	Bruckert 1999	3845	3	NA	France	RCT	Other	>90% pills taken	75%	Both	Unadjusted	75
Gender	Caspard 2005	4776	36	NA	USA	Cohort	Pharmacy records	≥80%	55%	Both	Age, sex, prior lipid-lowering therapy, baseline LDL	100
Gender	Chan 2010	14257	12	51.6 (8.33)	USA	Cohort	Pharmacy records	≥80%	36%	Both	Age, sex, income, race, comorbidities, concomitant medications, outpatient visits, ED visits, hospitalizations, physician characteristics, cost sharing	100
Gender	Chapman 2005	8406	36	NA	USA	Cohort	Pharmacy records	≥80% to both classes of medications	36%	Both	Age, sex, comorbidities, medical procedures, concomitant medications, outpatient visits, hospitalized days	100
Gender	Chapman 2008	4052	36	NA	USA	Cohort	Pharmacy records	≥80% to both classes of medications	33%	Both	Age, sex, comorbidities, concomitant medications, outpatient visits, hospitalized days, time between anti-hypertensive and anti-lipid medication	100
Gender	Cheng 2005	83	6	60.0 (13)	China	Cohort	Other	≥80% doses taken	84%	Both	Age, sex, SES, smoking status, comorbidities, baseline LDL, concomitant medications, medication characteristics	100

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Table I (*continued*)

Variable evaluated	Source	Sample size	Maximum duration (mo)	Mean age in years (SD)	Country	Design	Adherence measure	Adherence definition	Overall adherence	Prevention status*	Adjustment	Quality score (%)
Gender	Chodick 2008	229918	114	57.6 (NA)	Israel	Cohort	Pharmacy records	No medication gap >30 days and PDC ≥80%	29%	Both	Age, sex, SES, marital status, nationality, comorbidities, health services utilization, LDL levels	100
Gender	Corrao 2010	90832	66	61.8 (11.1)	Italy	Cohort	Pharmacy records	>75%	20%	Both	Unadjusted	75
Gender	Donnelly 2008	6462	156	62.8 (11)	Scotland	Cohort	Pharmacy records	≥80%	45%	Both	Age, sex, comorbidities, treatment duration, BMI, laboratory levels (LDL, total cholesterol, hemoglobin A1c), blood pressure, smoking status, concomitant medications	100
Gender	Foody 2008	186653	12	NA	USA	Cohort	Pharmacy records	No medication gap >60 d	50%	Both	Age, sex, insurance type, health care costs, geography, comorbidities, prior cardiovascular disease, physician specialty, concomitant medications	100
Gender	Gibson 2006	117366	18	58.8 (NA)	USA	Cohort	Pharmacy records	≥80%	53%	Both	Age, sex, insurance type, geography, urban residence, employee status, specialist visit, comorbidities, concomitant medications, mail order use, cost sharing	100
Gender	Helin-Salmivaara 2008	18072	120	NA	Finland	Cohort	Pharmacy records	No medication gap >270 d	71%	Both	Age, sex, SES, geography, comorbidities, concomitant medications	100
Gender	Jackevicius 2002	143506	24	NA	Canada	Cohort	Pharmacy records	20% grace period for refills	30%	Both	Age, sex, comorbidities, concomitant medications, physician visits	100
Gender	Ma 2008	1360	12	44.6 (NA)	Canada	Cohort	Pharmacy records	≥80%	39%	Both	Unadjusted	63
Gender	McGinnis 2007	435	12	59.5 (NA)	USA	Cohort	Pharmacy records	No medication gap >6 m	51%	Both	Unadjusted	75
Gender	Pedan 2007	6436	12	59.9 (13.1)	USA	Cohort	Pharmacy records	≥11 refills	13%	Both	Age, gender, comorbidities, geography, index prescription characteristics, provider characteristics	100
Gender	Perreault 2005b	17958	36	57.7 (4.0)	Canada	Cohort	Pharmacy records	No medication gap >60 d	71%	Both	Age, sex, comorbidities, SES, geography, concomitant medications, dosing schedule, healthcare utilization, primary prevention	100
Gender	Poluzzi 2008	137217	12	67.5 (10.1)	Italy	Cohort	Pharmacy records	≥300 tablets in 1 y	46%	Both	Age, sex, cardiovascular events, concomitant medications, LDL reduction	100
Gender	Schneeweiss 2007	41349	15	72.4 (NA)†	Canada	Cohort	Pharmacy records	No medication gap >90 d	59%	Both	Age, sex, income, comorbidities, statin duration, coronary heart disease, risk factors	100

Table I (*continued*)

Variable evaluated	Source	Sample size	Maximum duration (mo)	Mean age in years (SD)	Country	Design	Adherence measure	Adherence definition	Overall adherence	Prevention status*	Adjustment	Quality score (%)
Gender	Schultz 2005	21239	12	54 (10.5)	USA	Cohort	Pharmacy records	≥80%	43%	Both	Age, sex, comorbidities, co-payment, ischemic heart disease, outpatient visits, cholesterol tests, cardiovascular procedures, hospitalizations, ED visits, health care costs, prescription pattern	100
Gender	Shalansky 2002	367	6	61.4 (10.5)	Canada	Cohort	Pharmacy records	≥80%	88%	Both	Age, sex, concomitant medications, adverse effects, compliance aids, cardiology visits	88
Gender	Sung 1998	772	24	60.8 (9.4)	USA	Cohort	Pharmacy records	≥90%	37%	Both	Age, sex, ethnicity, education, employment status, marital status, medication regimen, health status, patient-provider interaction	100
Gender	Vinker 2008	47680	96	61.3 (11.8)	Israel	Cohort	Pharmacy records	≥80%	39%	Both	Age, sex, comorbidities, geography, country of origin, immigration year	100
Gender	Wei 2007	16363	60	NA	Scotland	Cohort	Pharmacy records	≥80%	555	Both	Unadjusted	75
Gender	Yang 2003	22408	84	NA	United Kingdom	Cohort	Pharmacy records	No medication gap >90 d	76%	Both	Age, sex, comorbidities, BMI, statin duration, smoking status, lipid-lowering class, physician visits, concomitant medications, cardiovascular disease	100
Gender	Yeaw 2009	94700	12	52.5 (9.1)	USA	Cohort	Pharmacy records	≥80% to 1 class	43%	Both	Age, sex, comorbidities, insurance type, copayment, geography, drug class, hospitalizations, concomitant medications	100
Gender	Yu 2008	19038	12	58.2 (11.6)	USA	Cohort	Pharmacy records	No medication gap >30 d	50%	Both	Age, sex, insurance type, physician specialty, comorbidities, physician visits, ED visits, hospitalizations, cardiac surgeries, prior lipoprotein or liver function test, concomitant medications, index statin	100
Race	Charles 2003	2000	18	NA	USA	Cohort	Pharmacy records	≥80%	73%	Both	Unadjusted	63
Race	Yood 2006	16052	12	59 (12.2)	USA	Cohort	Pharmacy records	≥80%	43%	Both	Unadjusted	75
Both	Batal 2007	3386	36	57.8 (10.9)	USA	Cohort	Pharmacy records	≥80%	47%	Both	Age, sex, race, comorbidities, insurance status, copayment	100
Both	Benner 2002	34501	120	74.4 (6)†	USA	Cohort	Pharmacy records	≥80%	39%	Both	Age, sex, race, comorbidities, medical procedures, insurance status, statin duration, concomitant medications, outpatient visits, hospitalized days	100

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Table I (*continued*)

Variable evaluated	Source	Sample size	Maximum duration (mo)	Mean age in years (SD)	Country	Design	Adherence measure	Adherence definition	Overall adherence	Prevention status*	Adjustment	Quality score (%)
Both	Ellis 2004	4802	48	59.7 (NA)	USA	Cohort	Pharmacy records	>90%	44%	Both	Age, sex, race, copayment, marital status, prevention status, dosing regimen, cardiology visits, LDL testing, prescription characteristics	100
Both	Kaplan 2004	510	48	64.4 (NA)	USA	Cross-sectional	Self-report	Regular medication use	88%	Both	Age, sex, race, SES, education, English-speaking, marriage status, health status, side effects, depression	86
Both	Yang 2009	962877	6	74.5 (10.2)	USA	Cohort	Pharmacy records	≥80%	54%	Both	Age, sex, race, comorbidities	100

Abbreviations: *NA*, Not available; *RCT*, randomized controlled trial; *LDL*, low-density lipoprotein; *BMI*, body mass index; *ED*, emergency department.
* Primary prevention, secondary prevention, or both.
† All patients in cohort are ≥65 years.

cardiovascular procedures as a result of patient preference, greater diagnostic and therapeutic uncertainty, stereotyping, and bias.[69] Evidence-based medications, including statins, are a cornerstone of cardiovascular risk reduction, and therefore, disparities in their use may also be important. Prior research has identified associations between sociodemographic characteristics and medication nonadherence.[12,70,71] However, the consistency and magnitude of this relationship have not been adequately studied.

The results of our meta-analysis support this hypothesis. Although overall rates of nonadherence to statins are very high, women had a 10% higher odds of nonadherence compared with men, and patients of nonwhite race were 53% more likely to be nonadherent compared with those of white race. The absolute and relative differences in adherence that we observed between nonwhite and white patients are likely to be clinically important. Although difficult to estimate precisely, patients who discontinue their medications after an acute MI are 3 times more likely to die than patients who remain adherent. Nonadherent diabetic patients experience rates of all-cause mortality that are 80% higher than their adherent counterparts.[10,11] Nonadherence is associated with a substantial economic cost. Health care costs are lower among adherent patients.[13] An estimated third of all medication-related hospital admissions are due to poor medication adherence, with resultant costs of $100 billion annually in the United States.[12,72]

Our results suggest that the magnitude of racial and gender disparities in nonadherence is as great or greater than those that have been observed for invasive cardiovascular procedures. Black patients with acute MI are 20% to 40% less likely than white patients to receive invasive cardiovascular procedures such as cardiac catheterization and percutaneous or surgical revascularization.[2,5,7] Compared with white men, white women are approximately 10% less likely and black women 25% less likely to undergo cardiac catheterization after acute MI.[73] A larger proportion of patients depend on medication therapy for primary and secondary prevention of cardiovascular disease than invasive procedures, supporting the hypothesis that efforts to reduce nonadherence may have a greater effect on health care disparities than efforts to address other evidence-based therapies. However, specific recommendations to identify and improve medication nonadherence, especially among vulnerable populations, are lacking in current clinical guidelines.

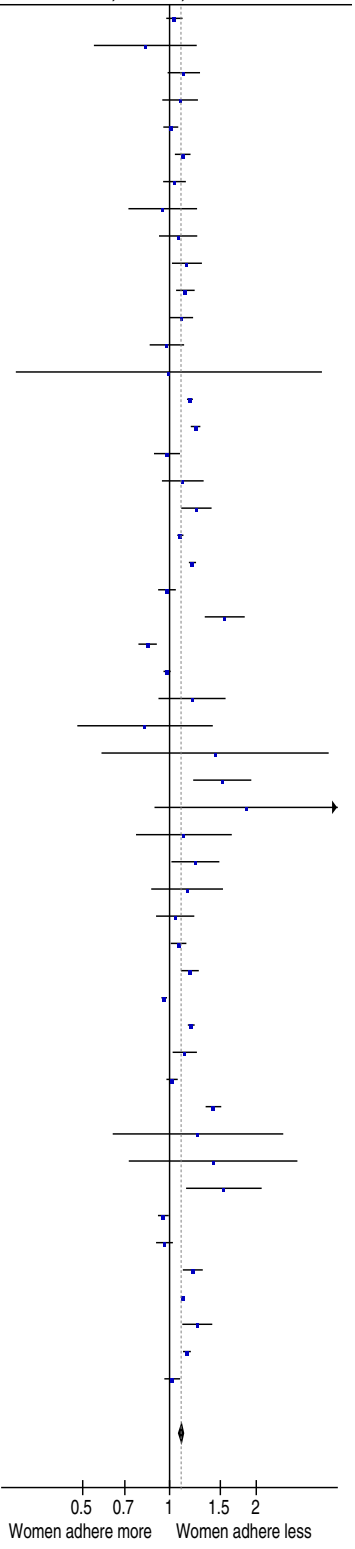
Our findings persisted in studies that adjusted for income, insurance status, copayment amounts, and other clinically important factors. This argues against the notion that the lower quality care received by women and nonwhite individuals is a reflection of variations in socioeconomic[74] or insurance status.[75] Among the 11 studies conducted in Canada, rates of nonadherence were similar among women and men. It is unclear whether this difference is explained by access to medications and health care or other demographic factors.

There are numerous potential reasons for the differential rates of adherence that we observed. For example, women and clinicians may not experience the same need to prioritize prevention of cardiovascular disease because of a misconception that women are at less risk.[76,77] Alternatively, women frequently serve as caregivers for family members, and caregivers frequently have lower rates of medication adherence.[78] In a standardized survey, half of women >50 years old reported that caregiving responsibilities were a major barrier to taking preventative action around cardiovascular health.[76] In subgroup analysis, women were no less adherent to statins compared with men in studies that reported medication persistence compared with medication adherence. This finding may be influenced by the wide range of time gaps used in the definition of persistence (30-270 days).

Figure 2

Study or Subgroup	Female Events	Female Total	Male Events	Male Total	Weight	Odds Ratio (Non-event) M-H, Random, 95% CI
Abraha 2003	2699	21419	2321	17803	2.7%	1.04 [0.98, 1.10]
Amin 2009	127	175	229	334	0.4%	0.82 [0.55, 1.24]
Avorn 1998	2066	5958	496	1329	2.0%	1.12 [0.99, 1.27]
Batal 2007	900	1932	708	1454	1.8%	1.09 [0.95, 1.25]
Benner 2002	10737	27566	2718	6935	2.8%	1.01 [0.96, 1.07]
Benner 2004	4050	9711	4301	9711	2.7%	1.11 [1.05, 1.18]
Benner 2005	1621	4831	1612	4679	2.4%	1.04 [0.96, 1.13]
Blackburn 2005	155	281	506	940	0.8%	0.95 [0.73, 1.24]
Bruckert 1999	1276	1715	1612	2130	1.7%	1.07 [0.92, 1.24]
Caspard 2005	1213	2280	1414	2496	2.1%	1.15 [1.03, 1.29]
Chan 2010	2242	6444	2948	7813	2.6%	1.14 [1.06, 1.22]
Chapman 2005	1366	3942	1643	4464	2.4%	1.10 [1.00, 1.20]
Chapman 2008	735	2220	598	1832	1.9%	0.98 [0.86, 1.12]
Cheng 2005	27	32	43	51	0.1%	1.00 [0.29, 3.36]
Chodick 2008	31749	116880	34484	113038	3.0%	1.18 [1.16, 1.20]
Corrao 2010	9855	53901	7978	36931	2.9%	1.23 [1.19, 1.27]
Donnelly 2008	1529	3380	1379	3082	2.3%	0.98 [0.89, 1.08]
Eagle 2004	1628	1881	3857	4396	1.6%	1.11 [0.95, 1.31]
Ellis 2004	863	2113	1240	2689	2.0%	1.24 [1.10, 1.39]
Foody 2008	42778	87571	50549	99082	3.0%	1.09 [1.07, 1.11]
Gibson 2006	26877	53509	34988	63857	3.0%	1.20 [1.17, 1.23]
Helin-Salmivaara 2008	5805	8164	7004	9908	2.6%	0.98 [0.92, 1.05]
Holme 2009	1448	1701	6461	7187	1.6%	1.55 [1.33, 1.81]
Hudson 2007	5556	7186	9673	13053	2.6%	0.84 [0.78, 0.90]
Jackevicius 2002	23488	77799	19564	65706	3.0%	0.98 [0.96, 1.00]
Jackevicius 2008	1945	2061	2410	2530	0.9%	1.20 [0.92, 1.56]
Kaplan 2004	250	281	199	229	0.3%	0.82 [0.48, 1.40]
Khanderia 2008	11	23	62	109	0.1%	1.44 [0.58, 3.55]
Kulkarni 2005	224	471	496	855	1.1%	1.52 [1.22, 1.91]
Ma 2008	10	39	514	1321	0.1%	1.85 [0.89, 3.82]
McGinnis 2007	104	208	120	227	0.5%	1.12 [0.77, 1.63]
McGinnis 2009	360	647	943	1554	1.3%	1.23 [1.02, 1.48]
Melloni 2009	243	348	530	729	0.8%	1.15 [0.87, 1.52]
Pedan 2007	400	3203	420	3233	1.7%	1.05 [0.90, 1.21]
Perreault 2005a	6223	12619	3954	7734	2.7%	1.08 [1.02, 1.14]
Perreault 2005b	4702	6824	8048	11134	2.6%	1.18 [1.10, 1.26]
Perreault 2009	92758	149674	56852	93240	3.0%	0.96 [0.94, 0.97]
Poluzzi 2008	29445	67236	33675	69981	3.0%	1.19 [1.17, 1.22]
Rasmussen 2007	6521	7474	9163	10349	2.3%	1.13 [1.03, 1.24]
Schneeweiss 2007	12013	20450	12378	20899	2.9%	1.02 [0.98, 1.06]
Schultz 2005	3001	8022	6068	13217	2.7%	1.42 [1.34, 1.50]
Shah 2009	52	69	119	150	0.2%	1.25 [0.64, 2.47]
Shalansky 2002	84	99	238	268	0.2%	1.42 [0.73, 2.76]
Sung 1998	116	369	167	403	0.7%	1.54 [1.15, 2.07]
Vinker 2008	10021	25392	8537	22288	2.9%	0.95 [0.92, 0.99]
Wei 2007	4134	7438	4872	8925	2.7%	0.96 [0.90, 1.02]
Yang 2003	5447	7329	6475	8333	2.5%	1.20 [1.12, 1.30]
Yang 2009	298422	568015	217680	394862	3.0%	1.11 [1.10, 1.12]
Ye 2007	1059	1831	2347	3717	2.1%	1.25 [1.11, 1.40]
Yeaw 2009	17641	42886	23080	51814	3.0%	1.15 [1.12, 1.18]
Yu 2008	3996	8044	5523	10994	2.7%	1.02 [0.97, 1.08]
Total (95% CI)		**1443643**		**1219995**	**100.0%**	**1.10 [1.07, 1.13]**
Total events	679972		603196			

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 915.37$, df = 50 ($P < .00001$); $I^2 = 95\%$
Test for overall effect: Z = 6.61 ($P < .00001$)

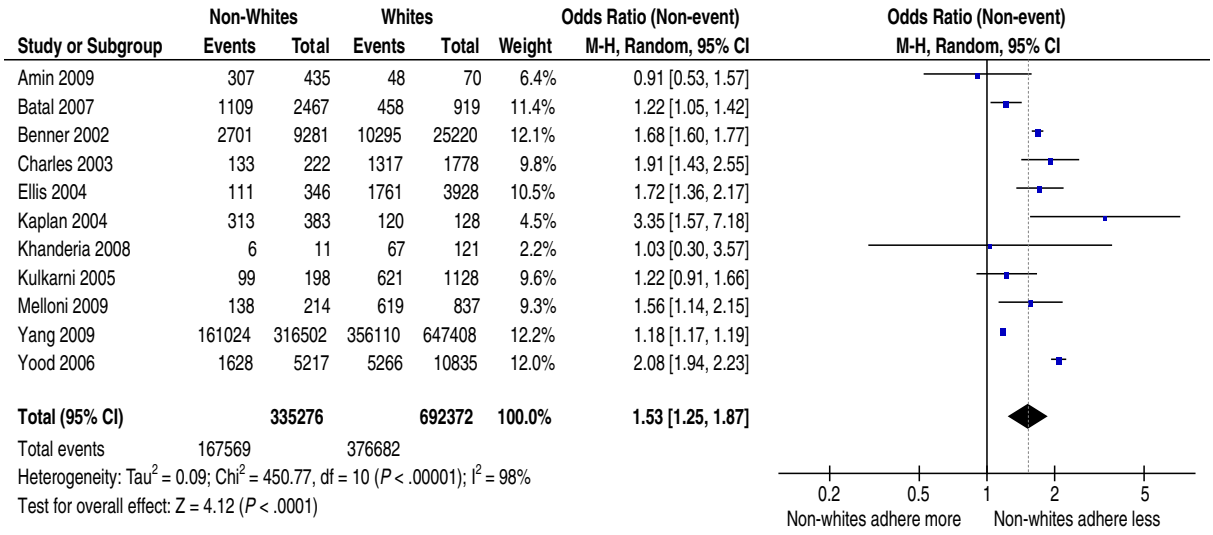


Plotted ORs (95% CIs) for statin nonadherence comparing women to men.

Table II. Odds ratio for nonadherence in women compared with men by subgroup

Characteristic	Subgroup	n	OR (95% CI)	I^2
Overall		51	1.10 (1.07, 1.13)	0.95
Adherence measure	Record review: adherence	32	1.12 (1.08, 1.16)	0.96
	Record review: persistence	12	1.04 (0.99, 1.10)	0.91
	Self-report	5	1.20 (1.0, 1.44)	0.45
	Other	2	1.07 (0.92, 1.24)	0
Geographic region	USA	26	1.13 (1.10, 1.17)	0.86
	Canada	11	1.02 (0.97, 1.08)	0.88
	Other	14	1.10 (1.04, 1.17)	0.94
Year of study publication	Before 2008	30	1.11 (1.05, 1.16)	0.92
	2008 or later	21	1.10 (1.05, 1.15)	0.96
Sample size	<10000 participants	27	1.14 (1.08, 1.20)	0.57
	≥10000 participants	24	1.08 (1.05, 1.12)	0.97
Prevention status	Primary	2	1.08 (0.91, 1.29)	0.99
	Secondary	13	1.16 (1.01, 1.33)	0.87
	Combined	36	1.10 (1.07, 1.13)	0.93
Analytic method	Univariable	13	1.10 (0.99, 1.22)	0.95
	Multivariable	38	1.11 (1.08, 1.14)	0.92
Adjustment for race	Yes	7	1.11 (1.05, 1.18)	0.72
	No	44	1.10 (1.06, 1.14)	0.95
Adjustment for socioeconomic status	Yes	20	1.11 (1.08, 1.15)	0.88
	No	31	1.09 (1.05, 1.15)	0.96
Age	Age ≥65 y	7	1.03 (0.99, 1.07)	0.63
	Age <and ≥65 y	44	1.11 (1.08, 1.15)	0.95
Quality	Quality score ≤75%	13	1.10 (0.99, 1.22)	0.95
	Quality score >75%	38	1.11 (1.08, 1.14)	0.92

Figure 3



Plotted ORs (95% CIs) for statin nonadherence comparing nonwhites to whites.

The reasons that nonwhite patients have lower rates of adherence are potentially more complex. Nonwhite patients are less likely to have a consistent relationship with a primary care provider compared with white patients with similar levels of insurance.[79] Furthermore, nonwhite patients are more likely to receive care from health care facilities that provide lower quality of care.[80,81] These factors may aggravate patient-level beliefs and attitudes that influence adherence, such as mistrust of the health care system, lack of knowledge of how to best use the health care system, and misunderstanding of provider instructions.[69] Women[82] and racial

Table III. Odds ratio for nonadherence in nonwhites compared with whites by subgroup

Characteristic	Subgroup	n	OR (95% CI)	I^2
Overall		10	1.53 (1.25, 1.87)	0.98
Year of study publication	Before 2008	7	1.67 (1.42, 1.97)	0.90
	2008 or later	4	1.22 (1.04, 1.42)	0.23
Adherence measure	Record review	7	1.51 (1.19, 1.91)	0.99
	Self-report	4	1.56 (1.08, 2.24)	0.53
Analytic method	Univariable	6	1.54 (1.18, 2.0)	0.78
	Multivariable	5	1.51 (1.19, 2.02)	0.98
Prevention status	Secondary	4	1.28 (1.04, 1.59)	0.06
	Combined	7	1.66 (1.31, 2.12)	0.99
Quality	Quality score ≤75%	5	1.45 (1.01, 2.09)	0.82
	Quality score >75%	6	1.49 (1.18, 1.87)	0.97

and ethnic minorities[83] may be more likely to experience side effects from statins, leading to early discontinuation or nonadherence.

General approaches to nonadherence may hold promise for women and nonwhite patients. A combination of patient education, medication reminders, and reinforcement forms the basis of successful adherence interventions and can be provided by physicians or affiliated healthcare staff.[84,85] Coordination of care and simplified dosing regimens may also be important.[86] Reducing barriers to care and patient cost sharing have been demonstrated to improve adherence.[87,88] The scale-up of electronic medical records offers unique opportunities for clinicians to receive timely information about pharmacy refill data, if such systems are designed with medication adherence in mind.[89] In addition, targeting characteristics that may be shared by vulnerable populations, such as health literacy, support systems, social stressors, and perception of the health care system, may be a particularly effective.[90] Furthermore, ongoing efforts to increase diversity in clinical training may increase the likelihood of a cultural match between vulnerable patients and clinical staff, which is important for patient outcomes and possibly for adherence as well.[69]

Quality of cardiovascular care has improved significantly over the past decade.[91,92] Significant differences in cardiovascular outcomes persist between white and nonwhite individuals; however, current trends suggest that disparities are narrowing.[91-93] Recent reductions in health disparities may be in part attributable to reductions in medication adherence disparities between white and nonwhite individuals. Further research needs to examine how the implementation of adherence interventions, exclusively or in combination, contributes to overall adherence, health care costs, and clinical outcomes.

Our study has several limitations. We combined studies with diverse patient populations, different adherence measurements, different types of statins, and varied durations of follow-up. One quarter of the studies did not conduct multivariable analyses. Those that did include multivariable analyses controlled for a variety of sociodemographic variables, but some important confounders, such as education or health literacy, were underrepresented. Most studies included patients taking statins for primary or secondary prevention, making it difficult to determine if the impact of race and gender on adherence differs by prevention status. Furthermore, it is difficult to identify the impact of treatment duration on adherence because many individuals included in the cohort studies were not statin naive.

Not all studies reported empirical data that could be included in the meta-analysis. In some cases, assumptions were made to include such data, such as overall adherence rates in the study population. Thus, small differences may exist between our calculations and those reported in the published reports. We aggregated patients of many races into a nonwhite race category. Individual analyses based on individual races would have been underpowered given the size of the studies including racial data. In addition, a large degree of heterogeneity existed between the studies, which was only partially explained in subgroup analyses. Among the subgroups that had less heterogeneity, as demonstrated by the lower I^2 score, the relationship between nonadherence and female gender and nonwhite race persisted.

Notwithstanding these limitations, our results demonstrate that women and racial minorities are at increased risk for nonadherence to statin therapy. The implementation of adherence interventions designed to address the needs of these populations offers an opportunity to reduce cardiovascular disparities.

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Disclosures

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Appendix. Full search strategy

((((‘adherence’ OR ‘non-compliance’ OR ‘adherence measures’ OR ‘prescription refill’ OR ‘medication refill’ OR ‘refill compliance’ OR ‘patient compliance’ OR ‘patient adherence’ OR ‘drug utilization’ OR ‘prescribed medication’ OR ‘pill count’ OR ‘cost-related underuse’ OR ‘treatment refusal’ OR ‘direct observed therapy’ OR ‘medication gaps’ OR ‘persistence’ OR ‘medication persistence’ OR ‘medication monitor’ OR ‘medication monitoring’) AND ‘hydroxymethylglutaryl coenzyme A reductase inhibitor’ OR hyperlipid* OR hypertriglycerid* OR cholestero* OR ‘anti-cholesterol’ OR ‘cholesterol lowering’ OR ‘HMG CoA reductase inhibitor’ OR ‘HMG CoA reductase inhibitors’ OR ‘HMG-CoA reductase inhibitor’ OR ‘HMG-CoA reductase inhibitors’ OR ‘statins’) AND Predictor OR Determinant OR Factor OR ‘Barriers’ OR ‘factors associated’ OR ‘Risk factors’ OR ‘Factors related’) AND ‘ethnic and racial groups’ OR Ethnic* OR ‘Race’ OR ‘Racial’ OR Black* OR ‘Hispanic’ OR ‘Latino’ OR ‘African American’ OR ‘African-American’ OR ‘Asian’ OR ‘Native’ OR ‘Aboriginal’ OR ‘Indian’ OR ‘Pacific’ OR ‘Subcontinent’ OR ‘Chicano’ OR ‘Mexican’ OR ‘Spanish’ OR ‘Indigenous’ OR ‘Minority’ OR ‘Underrepresented’ OR ‘Of color’ OR ‘Colored’ OR ‘Coloured’ OR ‘Of colour’ OR Sex OR ‘Gender’ OR ‘Sex’ OR ‘Women’ OR ‘Female’ OR ‘Male’ OR ‘Men’).